SECTION III.

AMENDMENT TO CLINICAL TRIAL REPORT: PROTOCOL PTL-0013/0022

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SECTION III.
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1.0 INTRODUCTION

This report is an amendment to the Study Report of protocol PTL-0013/0022, "Clinical Evaluation of Lubricoat 0.5% Ferric Hyaluronate Gel (INTERGEL®) for the Reduction of Adhesions Following Peritoneal Cavity Surgery, A Multicenter Study of Safety and Efficacy," dated March 4, 1999. The complete original final Study Report appears in Appendix D of this submission.

The objective of this multicenter, prospective, randomized, double-blind clinical trial was to compare the safety and efficacy of INTERGEL® Solution (formerly, Lubricoat) with lactated Ringer's solution in preventing or reducing the incidence, extent, and severity of post-surgical adhesions in patients following gynecological pelvic surgery throughout the abdominal cavity. The product was designed and intended as an adjunct to good surgical technique for this originally proposed indication. At present, there are no products approved for use in the United States (U.S.) as adjuncts to reduce the risk of post-surgical adhesions at sites other than the surgical site itself. As reflected in the original report, every efficacy endpoint prospectively identified and evaluated in this trial indicated a statistically significant difference between INTERGEL® Solution and the control treatment.

This amendment to the original Study Report of this trial was developed to provide a detailed presentation of a subset of the clinical trial results, inclusive of all subjects and focused on three of the identified efficacy endpoints described in the original Study Report. These efficacy endpoints are:

1. American Fertility Society (AFS) adhesion scores, reflecting adnexal adhesions (tubes and ovaries);

2. Surgical site adhesions; and

3. Reformed adhesions.

This amendment is provided in support of a proposed revised indication for use, based primarily on data for these clinically relevant endpoints. Although all of the data available from studies utilizing this product support the conclusion that it reduces incidence, extent, and severity of post-surgical adhesions throughout the abdominal cavity, a consideration of a subset of the 24 sites evaluated for adhesions (primarily the AFS adhesion score for adnexal adhesions) provides a means by which the trial results can be related to clinical utility. Adhesion scoring systems utilized in clinical medicine share a common approach—assessment of severity and extent of adhesions—but the AFS classification of adnexal adhesions is systematic and has been the method most widely utilized in clinical studies relating adhesions to patient outcome. A systematic review of the clinical literature regarding validation of the AFS score as a prognostic indicator for clinically relevant outcomes is provided in Appendix A.

Data on surgical site adhesions and reformed adhesions in this amendment supports the conclusion that the product is effective at preventing post-surgical adhesions. The clinical utility of surgical site adhesions and reformed adhesions is assumed not to be of concern within a regulatory context, given the precedents for approval of products based on these endpoints in the absence of patient outcome data. Additionally, reformed adhesions (beyond the surgical site) are assumed to be clinically relevant based on the decision by the attending surgeon to lyse adhesions observed upon first presentation.

Finally, this amendment provides an in-depth consideration of the important statistical analysis issues raised in the consideration of the results of this trial. Specifically, the rationale for utilizing data from all trial sites has been re-examined and considered in novel ways in order to minimize as much as possible the likelihood that the data gathered was biased by trial site. In addition, the originally proposed exploratory analysis of patients for whom data was not available at second-look laparoscopy (incomplete ascertainment) has been carefully re-examined. Although this analysis was never intended to supplant the evaluable patients as the primary efficacy population, execution of the original proposed approach *introduced bias* into the analysis because certain underlying assumptions were not met (primarily, that incomplete ascertainment is randomly distributed between groups). It has been possible to devise multiple alternative approaches to considering possible impact of incomplete ascertainment on the results of this trial. These approaches and the results obtained are presented herein. The result of the supplemental analysis of statistical issues does not alter the study findings; rather, from a statistical point of view, the rigor of the study evaluation has been enhanced.

2.0 STATISTICAL METHODS FOR ANALYSES INCLUDED IN AMENDMENT

The analyses described below focus primarily on adnexal adhesions in support of the product label, with secondary efficacy parameters also considered (surgical site adhesions, reformed adhesions). This section describes the analysis population groups, how the AFS scores were obtained from data in this trial, as well as the primary, secondary, and supplementary statistical analyses.

In all analyses, nonparametric tests were used since the data are categorical. Nonparametric tests are used to evaluate categorical data since there are no specific assumptions made with regard to one or more of the population parameters that characterize the underlying distribution(s) for which the test is employed (Sheskin 2000). Also in all analyses, two-sided p values are reported and p values less than 0.05 are considered to be statistically significant.

2.1 ANALYSIS GROUPS

The following population groups were evaluated for safety and effectiveness:

- The evaluable population consisted of all patients who received a second-look laparoscopic evaluation (n=265)[1], and
- All enrolled patients who received LUBRICOAT® Gel (INTERGEL® Solution) or lactated Ringer's solution were included in the safety analysis (n=281).

2.2 DEMOGRAPHIC, PRETREATMENT AND SURGICAL VARIABLES

Age, race, height, weight, previous and concomitant medications, presence of endometriosis, surgical procedures, estimated blood loss, operative time, baseline adhesion scores and length of hospital stay were summarized. Differences between the treatment groups were compared using Fisher's Exact test for the categorical data and Student's t-test for the continuous data. These analyses were performed for the evaluable population.

2.3 PRIMARY EFFICACY ANALYSES

The primary efficacy analysis was based on AFS adhesion score (see Table 2.1), providing for consideration of data for each patient by score and category. In the efficacy analysis, the failure rate in the INTERGEL® Solution subjects was compared to the failure rate in the control group (lactated Ringer's solution). A moderate or severe AFS adhesion category at second-look was considered a treatment failure in this study; *i.e.*, an AFS score of moderate (11-20) or severe (21-32) at second-look laparoscopy was a treatment failure. This definition of treatment failure is based on the consistent observations in the clinical literature that moderate/severe AFS adhesion scores are well-correlated with a poor fertility prognosis (Gomel and Erenus 1990, Nagata et al. 1997a, 1997b, Nagata 1998, Mage et al. 1986).[2] Treatment group comparisons were performed using the Cochran-Mantel-Haenszel Test in order to allow for stratification by baseline AFS classification using ridit scores. Because there are differing views on the choice of column scores for testing independence in ordered 2xK contingency tables, the modified method proposed by Graubard and Korn (1987) was also employed because this method preserves the underlying scoring system rather than converting values to ranks.

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[1] This definition of the evaluable population is consistent with the International Committee on Harmonisation (ICH) Guidance (in Section 5.2), approaches to the statistical evaluation of clinical trials described by experts (Pocok 1983, Meinert 1986), and regulatory precedents for FDA-approved Class III devices. See Section 4.0 of this document for details.

[2] The reader is referred to Appendix A for a systematic evaluation of the literature on adhesion scoring systems.

Table 2.1
AMERICAN FERTILITY SOCIETY PROGNOSTIC CLASSIFICATION FOR ADNEXAL ADHESIONS

Final AFS Score Range	Prognostic Classification for Adnexal Adhesions
0-5	Minimal
6-10	Mild
11-20	Moderate
21-32	Severe

Additional analyses were carried out using Fisher's exact test to compare the frequencies of patients having minimal (AFS score 0-5), mild (AFS score 6-10), moderate (AFS score 11-20), and severe (AFS score 21-32) scores for patients who received INTERGEL® Solution and patients who received lactated Ringer's solution. This comparison was made at baseline and also at second-look.

Finally, the primary efficacy analysis (failure vs. success) was also performed in subgroups of patients based on type of surgery performed at baseline. Again, treatment group comparisons were performed using the Cochran-Mantel-Haenszel test, in order to allow for stratification by baseline AFS adhesion score.

2.4 SUPPLEMENTAL ANALYSES

Supplemental analyses were carried out to respond to 1) concerns raised regarding the justification for combining data from all trial sites, particularly U.S. vs. European subjects, and 2) the use of a planned exploratory "intent-to-treat" efficacy population analysis that required the use of imputed values for patients with missing second-look laparoscopy data (incomplete ascertainment).

2.4.1 Use of Data from All Trial Sites

In order to confirm that data from all trial sites (U.S. and Europe) could be combined, analyses were performed to take into account the differences that existed between patients enrolled in the U.S. and patients enrolled in Europe. Potentially important differences in baseline characteristics between continents included race, adhesiolysis, operation time, days to discharge, days to second-look, and blood loss. For example, 38.3% of patients from the U.S. underwent baseline adhesiolysis, while 76.6% of patients from Europe underwent baseline adhesiolysis.

Key justifications for pooling of the data from both the U.S. and European clinical trial patients are discussed in detail in Section 3.0 (below), Justification for Use of Data from All Trial Sites.

In order to statistically confirm that the measures of effect (relative risks for the primary binary endpoint of success/failure) were consistent across the strata of concern (continent of enrollment and adhesiolysis subgroup) the Breslow-Day test of Homogeneity was performed (Section 3.2.1). Although the results of the Breslow-Day test demonstrated that data from all sites could be pooled, another supplementary analysis was conducted to ensure that the primary efficacy results were valid despite the differences between continents and in certain baseline characteristics. Thus, the primary analysis was carried out with stratification by continent of enrollment and adhesiolysis subgroup. The results of this supplementary analysis can be found in Section 3.0 (below), Justification for Use of Data from All Trial Sites.

In order to account for any differences between data obtained from the U.S. and European patients, the primary analysis was examined after stratifying by continent (U.S. vs. Europe; Section 3.2.2). To further account for differences that may exist between baseline rates of adhesiolysis between continents, the primary analysis was also stratified by adhesion subgroup. The adhesion subgroup variable had three categories: no baseline adhesiolysis, minimal or mild baseline adhesions (baseline AFS scores of 0 to 10) and moderate or severe baseline adhesions (baseline AFS scores of 11 to 32). Since adhesiolysis is highly correlated with the presence of baseline adhesions, stratification by adhesion subgroup takes into account any continental differences in adhesiolysis rates as well as baseline adhesion score.

2.4.2 Analyses to Address Incomplete Ascertainment of Second-Look Data

Use of imputed values for missing data (*i.e.*, an "intention to treat" population) in this pivotal trial, whereby the "worst" AFS adhesion score is assigned to patients with no second-look was originally proposed as an exploratory analysis. However, there was an unequal distribution of patients who discontinued from the study thereby introducing bias into this analysis: 12 patients who received INTERGEL® Solution discontinued but only 4 patients who received lactated Ringer's solution discontinued (p=0.084). Further, use of the worst case AFS adhesion score of 32 as the imputed value is not clinically justified, since this score was found on second-look laparoscopy in only 6 of 265 patients (all in the control group). Therefore, this proposed method for exploring the impact of incomplete ascertainment in this trial is not justified. Further detail is provided in Section 4.0 (below), Analysis of Incomplete Ascertainment Subject Data.

Nevertheless, in order to address the FDA request that analyses be conducted on the "intention to treat" population (n=281), four supplemental analyses were carried out on the primary efficacy variable of minimal or mild AFS adhesion scores vs. moderate or severe AFS adhesion scores in which imputed

values were applied, derived from four clinically and statistically justified techniques.

In the first two analyses, a bootstrapping technique was applied whereby numerous iterations of analyses with imputed values for missing second-look adhesion data were carried out. As noted previously, there were 12 patients in the INTERGEL® Solution group and 4 patients in the lactated Ringer's solution group who had no second-look laparoscopy. As described below, missing data for the primary efficacy variable was imputed for all 16 patients who had no second-look, and separately for a selected group of 7 patients who had no second-look, but for whom it could not be ruled out that a negative result had occurred. The second-look failure rate in lactated Ringer's solution control subjects (12.7%) obtained in the primary analysis of this amendment was utilized in these imputation analyses.

In the third analysis, a worse case AFS score of 32 was assigned to the 7 patients with no second-look laproscopy, who had clinical complaints. The primary analysis, stratified for adhesiolysis subgroup and continent, was then reexamined with these 7 patients included. The fourth analysis used a median AFS score that was calculated for each of the 4 AFS classification strata (minimal, mild, moderate, severe) for both the INTERGEL® Solution group and the lactated Ringer's group. The 7 patients were then assigned a median AFS score depending on which treatment they received. Sixteen different analyses were carried out in which the 4 INTERGEL® Solution patients received a median AFS score from one of the four strata (minimal, mild, moderate, severe) while the 3 control patients also received a median AFS score from one of the four strata (minimal, mild, moderate, severe). Once a median AFS score was assigned to each treatment group, the analyses were performed.

Details on each exploratory approach devised to address incomplete ascertainment of second-look data are provided below. The results of these analyses are presented in Sections 4.1.1 through 4.1.4.

2.4.2.1 Imputation Applying Control Group Failure Rate

The first method applied the 12.7% second-look failure rate found in the control group of this study to all 16 patients with no second-look laparoscopy. These 16 patients were randomly assigned as "failures" with a probability of 12.7%, and then the primary analysis was carried out on the population of 281 patients using a bootstrapping method. These simulated studies were carried out using the Cochran-Mantel-Haenszel test stratified for adhesiolysis group and continent and were repeated 1,000 times.

2.4.2.2 Imputation Applying Informed Censoring

The second method of imputation (informed censoring) excluded from the analysis the 9 patients (patient identification numbers 205, 243, 501, 1102, 1112, 1202, 2110, 2129, 2135) who had refused second-look laparoscopy, but had no problems or complaints. The reason for each patient's discontinuation is listed in Table 5.5 of the Study Results section of this amendment. Thus, the 12.7% second-look failure rate found in the control group of this study was applied to the 7 patients with no second-look laparoscopy, who had clinical complaints (patient identification numbers [redacted]). These 7 patients were randomly assigned as "failures" with a probability of 12.7%, and then the primary analysis was carried out on the population of 272 patients using a bootstrapping method. These simulated studies were carried out using the Cochran-Mantel-Haenszel test stratified for adhesiolysis group and continent, and were repeated 1,000 times.

2.4.2.3 Imputation Applying Worst Case AFS Scores

The third method of imputation (informed censoring) assigned a score of 32 (worst case) to the 7 patients with no second-look laproscopy, who had clinical complaints. Excluded from the analysis were the 9 patients (patient identification numbers [redacted]) who had refused second-look laparoscopy but had no problems or complaints. The reason for each patient's discontinuation is listed in Table 5.5 of the Study Results section of this amendment. The primary analysis was carried out on the population of 272 patients using the Cochran-Mantel-Haenszel test stratified for adhesiolysis group and continent.

2.4.2.4 Additional Imputations Using Various AFS Scores

The fourth method of imputation (informed censoring) also excluded patients who had refused second-look laparoscopy but did not report any problems or complaints. Excluded from the analysis were the 9 patients (patient identification numbers [redacted]) who had refused second-look laparoscopy but had no problems or complaints. The reason for each patient's discontinuation is listed in Table 5.5 of the Study Results section of this amendment. In this imputation analysis, these 7 patients were given a median AFS score that was

determined in each of the 4 AFS classification strata (minimal, mild, moderate, severe) for both the INTERGEL® Solution group and lactated Ringer's group. For example, as shown in scenario "A" of Table 2.2 the median minimal score for lactated Ringer's patients was assigned to the 3 lactated Ringer's patients with missing second-look data and the median minimal score for INTERGEL® Solution patients was assigned to the 4 INTERGEL® Solution patients with missing data, and the analysis was re-run with these 7 patients included. As another example, as shown in scenario "O" of Table 2.2 the median severe score for lactated Ringer's patients was assigned to the 3 lactated Ringer's patients with missing second-look data and the median moderate score for INTERGEL® Solution patients was assigned to the 4 INTERGEL® Solution patients with missing data and the analysis was re-run with these 7 patients included. A total of 16 scenarios were carried out based on this method of assigning scores to the 7 patients with missing second-look data who had clinical complaints. For each simulated study, treatment group comparisons were performed on the 272 patients using the Cochran-Mantel-Haenszel Test in order to allow for stratification by baseline AFS classification using ridit scores. Because there are differing views on the choice of column scores for testing independence in ordered 2xK contingency tables, the method proposed by Graubard and Korn (1987) was also employed because this method preserves the underlying scoring system rather than converting values to ranks.

Table 2.2
16 DIFFERENT IMPUTATION ANALYSES

		INTERGEL® Solution Patients			
		Minimal	**Mild**	**Moderate**	**Severe**
Control Patients	**Minimal**	A	B	C	D
	Mild	E	F	G	H
	Moderate	I	J	K	L
	Severe	M	N	O	P

2.5 SECONDARY EFFICACY ANALYSES

Secondary efficacy variables examined in this amendment were the assessment of surgical site adhesions and reformed adhesions. These data, as with the AFS score data, were presented in the original Study Report (Appendix D).

The proportion of surgical site adhesions at second-look was determined for each patient. This proportion was compared between the INTERGEL® Solution group and the lactated Ringer's solution group using the Student's t-test.

Reformed adhesions included adhesions lysed during the first surgery that reformed and were present during the second-look laparoscopy. The proportion of reformed adhesions was determined for each patient during the second-look surgery. This proportion was compared between the INTERGEL® Solution group and the lactated Ringer's solution group using the Student's t-test.

3.0 JUSTIFICATION FOR USE OF DATA FROM ALL TRIAL SITES

The INTERGEL® Solution trial was conducted at 11 sites in the U.S. and at 5 sites in Europe according to a single protocol. Justifications, both clinical and statistical, for combining the data from both the U.S. and European clinical trial centers are provided below.

3.1 CLINICAL RATIONALE

3.1.1 Rigor of Study Design

The first clinical justification for the pooling of data from all clinical sites is that the INTERGEL® Solution pivotal trial was a well-designed, randomized clinical trial. Meinert (1986) states that the "basis for pooling treatment results across clinics in a multicenter trial . . . stems from the use of common treatment and data collection procedures, and from ongoing quality assurance procedures designed to detect and minimize procedural differences among study clinics." Randomization is the gold standard for eliminating selection bias in the assignment of individuals to study and control groups. This trial incorporated the most critical design features for a surgical trial intended to minimize bias and to control for confounding variables. Additionally, although identified under two protocol numbers, PTL-0013 and PTL-0022, patients were enrolled or eliminated from participation under the same inclusion/exclusion criteria and followed identical procedures in the U.S. and Europe.

3.1.2 Even Distribution of Baseline Characteristics between Treatment Groups

There were no significant differences between the INTERGEL® Solution and lactated Ringer's solution groups in baseline clinical characteristics, patient characteristics, or surgical parameters (refer to Tables 5.6-5.9 of Section 5.0 below). When the randomized clinical trial population was separated into its U.S. and European cohorts, differences were seen in race, adhesiolysis, operation time, days to discharge, days to second-look, and blood loss. By definition, these variables would only be considered confounders if they were distributed differently between the treatment and control groups and were related to the outcome (Riegelman and Hirsch 1996). Furthermore, it is important to note that baseline adhesion assessment took place after the patient was randomized and surgery had begun.

3.2 STATISTICAL RATIONALE

3.2.1 Test for Homogeneity

In order to justify that the measure of effect (relative risk for the primary binary endpoint of success/failure) is consistent across the strata of concern, the Breslow-Day test of Homogeneity was performed. The strata of concern, based on comments from FDA, include continent of enrollment (U.S. or Europe) and adhesiolysis subgroup. The three adhesiolysis subgroup categories were: no baseline adhesiolysis, minimal or mild baseline adhesions (baseline AFS scores of 0-10) and moderate or severe baseline adhesions (baseline AFS scores of 11 to 32). When stratified by both continent and adhesiolysis category, the Breslow-Day test of Homogeneity was not statistically significant (p=0.5682). Stratifying by adhesiolysis category, the Breslow-Day test of Homogeneity was not statistically significant (p=0.4985). The lack of statistical significance indicates that the continent-specific estimates are homogeneous and the adhesiolysis subgroup-specific estimates are homogeneous. Therefore, it is appropriate to pool these data since "data are within sampling variation of each other" (Hosmer and Lemeshow 1989).

3.2.2 Stratified Primary Efficacy Analysis

In can be concluded, based on the above data and analyses, that inclusion of data from all sites in this trial is appropriate. To further confirm this conclusion, the primary efficacy variable (success/failure) was stratified by the two variables of concern to FDA: continent and adhesiolysis. When the primary analysis of success/failure was stratified by these variables, the differences between treatment and control remained statistically significant as shown in Table 3.1.

Table 3.1
PERCENTAGE OF PATIENTS WITH MODERATE OR SEVERE SCORES AT SECOND-LOOK (STRATIFIED BY CONTINENT OF ENROLLMENT AND ADHESIOLYSIS CATEGORY)

			INTERGEL® Solution		Lactated Ringers		Relative		
Continent	Adhesiolysis	Center	n / N	Percent	n / N	Percent	Risk	95% CI	p
U.S.	None	All	1/ 58	1.7	4/ 58	6.9	0.250	0.034 to 1.828	0.1721
U.S.	Minimal/Mild	All	2/ 30	6.7	4/ 30	13.3	0.500	0.102 to 2.456	0.3934
U.S.	Moderate/Severe	All	0/ 5	0.0	3/ 7	42.9	0.000		0.1056
Europe	None	All	0/ 7	0.0	0/ 11	0.0			
Europe	Minimal/Mild	All	0/ 27	0.0	2/ 18	11.1	0.000		0.0798
Europe	Moderate/Severe	All	0/ 4	0.0	4/ 10	40.0	0.000		0.1492
All*	All*	All	3/131	2.3	17/134	12.7	0.198	0.067 to 0.581	0.0032
All	None	All	1/ 65	1.5	4/ 69	5.8	0.265	0.036 to 1.976	0.1953
All	Minimal/ Mild	All	2/ 57	3.5	6/ 48	12.5	0.281	0.066 to 1.192	0.0851
All	Moderate/Severe	All	0/ 9	0.0	7/ 17	41.2	0.000		0.0272
All	All**	All	3/131	2.3	17/134	12.7	0.188	0.063 to 0.560	0.0027
All	All	All***	3/131	2.3	17/134	12.7	0.181	0.063 to 0.516	0.0014

Blanks indicate that the value could not be calculated, p values: Cochran-Mantel-Haenszel Test, Relative Risk: Mantel-Haenszel Method

* Stratified by Continent and Adhesiolysis Category (Breslow-Day test of Homogeneity: p = 0.5682)

** Stratified by Adhesiolysis Category (Breslow-Day test of Homogeneity: p = 0.4985)

*** Not Stratified

4.0 ANALYSIS OF INCOMPLETE ASCERTAINMENT SUBJECT DATA

The second statistical issue is consideration of the most meaningful and rigorous approach to evaluating subjects who failed to have a second-look laparoscopy. This study, as is typical for surgical trials, was prospectively designed and powered to include evaluable subjects in the effectiveness analysis, and all subjects in the safety analysis. For surgical trials, a high degree of discontinuations and/or subjects lost-to-follow-up are expected. One reason for this is the long duration of pivotal trials required for regulatory approval (1 to 2 years of follow-up prior to approval for most implants or invasive procedures; and long-term follow-up in some cases requiring post-marketing cohorts). FDA assumes, for example, that subjects enrolled in studies of total knee replacements, for which 24 month follow-up data is required, will be lost at a rate of about 20% (Van Vleet 1998). For breast implants, sponsors can expect a 40% dropout rate over a 10-year period.

A second important reason that surgical trials are expected to have discontinuations is that subjects will refuse to return or participate in a follow-up visit, especially if it requires an invasive procedure and/or they have no complications. This is particularly true for elective surgeries, as opposed to trials of pharmaceuticals for which mortality is the outcome measured (Dorey 1998, Kuntz et al. 1993).

It is important to recognize that a statistical principle applied to trials of pharmaceuticals, which requires that all patients randomized be included in the primary data analysis, is a mechanism for reducing bias which may be introduced by incomplete adherence or compliance to the protocol by the subject, and thereby mimic as closely as possible the conditions that may occur in actual medical practice. This rationale is rarely relevant to surgical trials.

For these reasons, in the absence of a valid rationale for concluding that discontinued subjects, or subjects lost-to-follow-up, have a worse outcome than those who complete the study, protocols for the analysis of medical device trials most often do not include imposition of imputed results for non-completers. The practice of incorporating imputed values for missing data in surgical trials as a condition of approval in the analysis of primary efficacy data has, to the sponsor's knowledge, been applied rarely, if at all, by FDA. There is no requirement for use of imputed values to compensate for incomplete ascertainment in the draft FDA Guidance on Resorbable Adhesion Barriers (1999), nor has this practice been required in the analysis of pivotal trials supporting approvals of original PMAs for cardiovascular, soft tissue, orthopedic, or neurologic implants.

For the INTERGEL® Solution trial, the number of subjects who did not have second-look laparoscopy was small, but there was a significant difference (8.4% vs. 2.9%) between groups (treatment vs. control, respectively). Because the incomplete ascertainment of data was not random, arbitrary use of a single imputed value for each instance will produce selection bias (Meinert 1986). Further, use of the worst case AFS adhesion score of "32" as the imputed value in an exploratory analysis of these data is not clinically justified since this score was found on second-look laparoscopy in only 6 of

265 patients. In addition, all 6 patients with a score of "32" received the lactated Ringer's solution. Results of this originally designed exploratory analysis have been previously presented (see Study Report, Appendix D).

4.1 IMPUTATION OF MISSING SECOND-LOOK SURGERY DATA IN THE INTERGEL® SOLUTION PIVOTAL TRIAL

At the request of FDA and, as an exploratory statistical evaluation, the sponsor agreed to include imputed values for subjects who failed to have second-look laparoscopy. Since application of the originally proposed methodology introduces bias, alternative approaches to this exploratory analysis have been developed. The statistical community is not in agreement concerning the most appropriate analysis method when there is missing data (Pocock 1983, Meinert 1986, Friedman et al. 1985) except to indicate that multiple analyses should be conducted to determine the robustness of the result. The rationale for performing multiple evaluations is to determine if the conditions for which the study results hold are a small subset of the total analyses or if there is a preponderance of evidence to support the study outcome. The agreed to exploratory analysis is but one of these evaluations of the strength of the result.

The ICH (1998) states that imputation techniques ranging from carrying forward the last observation to the use of complex mathematical models may be used in an attempt to compensate for missing data. The ICH also states that it is important to demonstrate the robustness of the corresponding results of analysis especially when the strategy in question could itself lead to biased estimates of treatment effects. Since the data is missing, any imputation is likely to lead to bias, but the direction and size of the bias is unknown. Thus, if the result is robust across a number of likely scenarios, one could argue that the bias is minimal or too small to influence the study conclusions. It has also been stated by Meinert (1986) that "while there is no substitute for complete follow-up, the usual approach is to carry out a series of analyses, each requiring a different set of assumptions regarding the rate of outcome events after patients are lost to follow-up. One of the analyses should be done assuming a zero event rate over the periods patients are lost to follow-up. Other analyses may be done in which all patients lost to follow-up are assumed to have had an event after loss to follow-up, or alternatively, in which they are assumed to have experienced the event at the same rate as a defined proportion of the study population (e.g., the control-treatment group of patients who remained under active follow-up). Losses are not a serious source of concern if the various analyses all support the same basic conclusion and if they are not differential by treatment group."

Taking into consideration the information provided by ICH and statements from Meinert on how to deal with incomplete ascertainment, several analyses were performed using the primary efficacy variable of treatment failure where missing second-look data were imputed under statistically reasonable and clinically justifiable assumptions. In the first three analyses, the primary efficacy analysis remained statistically significant. In the fourth analysis, the primary efficacy analysis remained statistically significant in 15 of the 16 imputation analyses performed when using ridit

scores and all 16 imputation analyses were statistically significant when using the median scores based on the method described by Graubard and Korn (1987).

Each of the four approaches is described and the results presented below.

4.1.1 Imputation by Control Group Failure Rate

The first analysis applied a 12.7% failure rate to all 16 patients who did not complete the second-look procedure and were discontinued from the study. The 12.7% failure rate is the failure rate observed in the lactated Ringer's solution group. By randomly imputing these 16 patients as failures with a probability of 12.7%, a conservative, yet clinically valid failure rate was employed. Thus, 1,000 simulations were performed using a bootstrapping method assuming a 12.7% failure rate for patients who did not undergo the second-look procedure (see Section 2.5.2.1).

For each simulated study, the results were analyzed using the Cochran-Mantel-Haenszel test, stratified by continent and adhesiolysis group. The median p-value of the 1,000 simulations of the Cochran-Mantel-Haenszel test was 0.006 (95% confidence interval: 0.001-0.035). The median relative risk of the 1,000 analyses comparing the failure rate of INTERGEL® Solution to the failure rate of lactated Ringer's solution was 0.262 (95% confidence interval, 0.176-0.400). This exercise of conservative imputation of missing data clearly supports the primary results of this trial: INTERGEL® Solution is significantly more effective than lactated Ringer's solution in reducing post-surgical adnexal adhesions.

4.1.2 Imputation by Informed Censoring

The second method of imputation analysis is referred to as informed censoring because it takes into account the reason patients discontinued from the study. This analysis excluded patients who had refused second-look laparoscopy, but did not report any problems or complaints. Table 5.5 of the Study Results section of this amendment lists the randomized patients for whom a second-look laparoscopy was not performed, and the reason for discontinuation of the study. It was determined that 7 out of the 16 patients dropped out of the study for reasons that could not rule out a clinically negative outcome (patients [redacted]). In this imputation analysis, these 7 patients were randomly imputed as failures with a probability of 12.7% as before, and 1,000 simulations were performed using a bootstrapping method procedure (see Section 2.5.2.2).

For each simulated study, the results were again analyzed using the Cochran-Mantel-Haenszel test, stratified by continent and adhesiolysis group. The median p-value of the 1,000 simulations of the Cochran-Mantel-Haenszel test was 0.003 (95% confidence interval: 0.002-0.016). The median relative risk

of the 1,000 analyses comparing the failure rate of INTERGEL® Solution to the failure rate of lactated Ringer's solution was 0.199 (95% confidence interval, 0.187-0.317). Again, this exercise of imputation of missing data in those patients with insufficient clinical evidence of good health, supports the primary results of this trial.

4.1.3 Imputation by Worst Case AFS Score

The third method of imputation analysis is also a type of informed censoring. This analysis excluded patients who had refused second-look laparoscopy but did not report any problems or complaints. Table 5.5 of the Study Results section of this amendment lists the randomized patients for whom a second-look laparoscopy was not performed, and the reason for discontinuation of the study. It was determined that 7 out of the 16 patients dropped out of the study for reasons that could not rule out a clinically negative outcome (patients [redacted] The 7 patients who dropped out of the study for reasons that could not rule out a clinically negative outcome were assigned a worst case AFS score of 32.

The primary analysis was carried out on the population of 272 patients using the Cochran-Mantel-Haenszel test stratified for adhesiolysis group and continent. It was determined that all stratified analyses remained statistically significant as shown in Table 4.1.

Table 4.1
PERCENTAGE OF PATIENTS WITH MODERATE OR SEVERE SCORES AT SECOND-LOOK (STRATIFIED BY CONTINENT AND ADHESIOLYSIS CATEGORY - WORST CASE AFS SCORE)

			INTERGEL® Solution		Lactated Ringers		Relative		
Continent	Adhesiolysis	Center	n / N	Percent	n / N	Percent	Risk	95% CI	p
U.S.	None	All	3/ 60	5.0	5/ 59	8.5	0.590	0.150 to 2.327	0.4511
U.S.	Minimal/Mild	All	3/ 31	9.7	6/ 32	18.8	0.516	0.145 to 1.838	0.3074
U.S.	Moderate/Severe	All	0/ 5	0.0	3/ 7	42.9	0.000		0.1056
Europe	None	All	0/ 7	0.0	0/ 11	0.0			
Europe	Minimal/Mild	All	1/ 28	3.6	2/ 18	11.1	0.321	0.035 to 2.975	0.3174
Europe	Moderate/Severe	All	0/ 4	0.0	4/ 10	40.0	0.000		0.1492
All*	All*	All	7/135	5.2	20/137	14.6	0.375	0.166 to 0.844	0.0178
All	None	All	3/ 67	4.5	5/ 70	7.1	0.627	0.157 to 2.495	0.5076
All	Minimal/Mild	All	4/ 59	6.8	8/ 50	16.0	0.424	0.141 to 1.277	0.1272
All	Moderate/Severe	All	0/ 9	0.0	7/ 17	41.2	0.000		0.0272
All	All**	All	7/135	5.2	20/137	14.6	0.366	0.163 to 0.824	0.0153
All	All	All***	7/135	5.2	20/137	14.6	0.355	0.162 to 0.777	0.0096

Blanks indicate that the value could not be calculated, p values: Cochran-Mantel-Haenszel Test, Relative Risk: Mantel-Haenszel Method

* Stratified by Continent and Adhesiolysis Category (Breslow-Day test of Homogeneity: p = 0.6155)

** Stratified by Adhesiolysis Category (Breslow-Day test of Homogeneity: p = 0.2654)

*** Not Stratified

4.1.4 Additional Imputations Using Various AFS Scores

The fourth method of imputation utilized informed censoring, which excluded patients who had refused second-look laparoscopy but did not report any problems or complaints. Table 5.5 of the Study Results section of this amendment lists the randomized patients for whom a second-look laparoscopy was not performed, and the reason for discontinuation of the study. It was determined that 7 out of the 16 patients dropped out of the study for reasons that could not rule out a clinically negative outcome (patients 208, 222, 234,1115, 1125, 1217, 2307).

In this imputation analysis, these 7 patients were given a median AFS score that was determined in each of the 4 AFS classification strata (minimal, mild, moderate, severe) for both the INTERGEL® Solution group and the lactated Ringer's group. For example, as shown in scenario "A" of Table 4.2, the median minimal score for lactated Ringer's patients was assigned to the 3 lactated Ringer's patients with missing second-look data and the median minimal score for INTERGEL® Solution patients was assigned to the 4 INTERGEL® Solution patients with missing data and the analysis was re-run with these 7 patients included. As another example, scenario "O" of Table 4.2 demonstrates that the median severe score for lactated Ringer's patients was assigned to the 3 lactated Ringer's patients with missing second-look data and the median moderate score for INTERGEL® Solution patients was assigned to the 4 INTERGEL® Solution patients with missing data and the analysis was re-run with these 7 patients included. A total of 16 scenarios were carried out based on this method of assigning scores to the 7 patients with missing second-look data who had clinical complaints.

For each of the 16 simulated scenarios, treatment group comparisons were performed on the 272 patients using the Cochran-Mantel-Haenszel Test in order to allow for stratification by baseline AFS classification using ridit scores. Because there are differing views on the choice of column scores for testing independence in ordered 2xK contingency tables, the modified method proposed by Graubard and Korn (1987) utilizing medians was also employed because this method preserves the underlying scoring system rather than converting values to ranks. It was determined that the primary efficacy analysis remained statistically significant in 15 of the 16 imputation analyses performed when using median scores and all 16 imputation analyses were significant when using ridit scores. This further validates the statement by ICH that if the result is robust across a number of likely scenarios, one could argue that the bias is not important to the study outcome. The only imputation analysis performed that was not statistically significant when using median scores was scenario "D" in which the median minimal score for lactated Ringer's patients was assigned to the 3 lactated Ringer's patients with missing second-look data and the median severe score for INTERGEL® Solution patients was assigned to the 4 INTERGEL® Solution patients with missing

data. This scenario, in which all three lactated Ringer's patients received a minimum median score and the INTERGEL® Solution patients all received a severe median score is highly unlikely and would most likely not be the true distribution of scores that would have been observed if these 7 patients completed the study.

Table 4.2
16 DIFFERENT IMPUTATION ANALYSES

		INTERGEL® Solution Patients			
		Minimal	**Mild**	**Moderate**	**Severe**
Control Patients	**Minimal**	A	B	C	D
	Mild	E	F	G	H
	Moderate	I	J	K	L
	Severe	M	N	O	P

5.0 STUDY RESULTS: ANALYSIS OF EFFECTIVENESS

5.1 RANDOMIZED PATIENTS AND THEIR DISPOSITION

5.1.1 Randomized Patients

A total of 303 patients were randomized at 11 centers in the U.S. and 5 in Europe. The number of patients randomized at each center ranged from 1 to 53. The distribution of randomized patients is shown by treatment group and investigational center in Table 5.1. In general, there were similar numbers of patients randomized to INTERGEL® Solution and lactated Ringer's solution at each site.

Table 5.1
NUMBER AND PERCENT OF PATIENTS RANDOMIZED AT EACH CENTER[3]

	INTERGEL® Solution		Lactated Ringer's Solution		Total	
Center No.	N	%	N	%	N	%
United States						
02	27	17.8	26	17.2	53	17.5
03	6	3.9	6	4.0	12	10.0
04	4	2.6	3	2.0	7	2.3
05	1	0.7	-	-	1	0.3
06	6	3.9	9	6.0	15	5.0
07	5	3.3	6	4.0	11	3.6
08	7	4.6	7	4.6	14	4.6
09	12	7.9	11	7.3	23	7.6
10	14	9.2	13	8.6	27	8.9
11	20	13.2	19	12.6	39	12.9
12	7	4.6	10	6.6	17	5.6
Total	109	71.7	110	72.8	219	72.3
Europe						
21	14	9.2	15	9.9	29	9.6
23	11	7.2	9	6.0	20	6.6
25	7	4.6	8	5.3	15	5.0
27	5	3.3	3	2.0	8	2.6
29	6	3.9	6	4.0	12	4.0
Total	43	28.3	41	27.2	84	27.7
All Centers	152	100.0	151	100.0	303	100.0

[3] Reproduced from Table 6.1 of the Clinical Trial Report, March 4, 1999

5.1.2 Patient Disposition

Of the 303 randomized patients, 22 did not receive treatment (INTERGEL® Solution or lactated Ringer's solution under the protocol) and 281 were treated. The disposition of patients who were randomized but not treated is summarized in Table 5.2. The group to which patients randomized but not treated were to be assigned was not known at the time the inclusion/exclusion decision was made. The majority of these patients did not meet the intra-operative criteria and were subsequently excluded from study participation. These 22 subjects were not included in any further tables or analyses.

Table 5.2
DISPOSITION OF RANDOMIZED PATIENTS WHO WERE NOT TREATED: NUMBER (%) OF PATIENTS[4]

	INTERGEL® Solution	Lactated Ringer's Solution	Total
Total randomized but not treated	9 (100.0)	13 (100.0)	22 (100.0)
Reason for not receiving treatment			
Did not meet intra-operative criteria	9 (100.0)	11 (84.6)	20 (91.0)
Lost to follow-up*	0 (0.0)	1 (7.7)	1 (4.5)
Physician decision	0 (0.0)	1 (7.7)	1 (4.5)

* Patient was scheduled for surgery but canceled and went to another hospital for treatment.

[4] Reproduced from Table 6.2 of the Clinical Trial Report, March 4, 1999

More specific reason(s) for not treating patients who were randomized are provided in Table 5.3.

Table 5.3
LIST OF RANDOMIZED PATIENTS WHO WERE NOT TREATED[5]

Patient Identification	Site No.	Reason for Not Being Treated
Patients randomized to INTERGEL® Solution		
[redacted]	2	Left salpingo-oophorectomy was performed
[redacted]	2	Surgical Seprafilm used
[redacted]	2	Extensive adhesions, patient potentially had ovarian cancer
[redacted]	8	Salpingo-oophorectomy was performed
[redacted]	11	Patient diagnosed with ovarian cancer
[redacted]	12	Twelve or more of the 24 anatomical sites involved with adhesions
[redacted]	12	GI resection performed during surgery to excise endometriosis
[redacted]	25	Twelve or more of the 24 anatomical sites involved with adhesions
[redacted]	25	Twelve or more of the 24 anatomical sites involved with adhesions
Patient randomized to lactated Ringer's solution		
[redacted]	2	Salpingo-oophorectomy was performed
[redacted]	2	Patient refused second-look procedure and went to another hospital
[redacted]	2	Interceed was used
[redacted]	2	Twelve or more of the 24 anatomical sites involved with adhesions
[redacted]	2	Twelve or more of the 24 anatomical sites involved with adhesions, left ovary and fallopian tubes were removed
[redacted]	2	Patient had serious papillary cystadenoma and ovarian cancer present
[redacted]	3	Insulin dependent diabetic
[redacted]	6	Twelve or more of the 24 anatomical sites involved with adhesions
[redacted]	9	Twelve or more of the 24 anatomical sites involved with adhesions
[redacted]	11	Twelve or more of the 24 anatomical sites involved with adhesions
[redacted]	11	Patient did not have a uterus
[redacted]	12	Twelve or more of the 24 anatomical sites involved with adhesions
[redacted]	29	Twelve or more of the 24 anatomical sites involved with adhesions

[5] Adapted from Table 6.3 of the Clinical Trial Report, March 4, 1999 (order of presentation different)

Of the 281 randomized patients who received treatment, 265 completed the study, and 16 did not complete the second-look procedure and were discontinued from the study. The disposition of randomized patients who received treatment is summarized by treatment group in Table 5.4.

Table 5.4
DISPOSITION OF RANDOMIZED PATIENTS WHO RECEIVED TREATMENT: NUMBER (%) OF PATIENTS[6]

	INTERGEL® Solution	Lactated Ringer's Solution	Total
Total randomized and treated	143 (100.0)	138 (100.0)	281 (100.0)
Completed study	131 (91.6)	134 (97.1)	265 (94.3)
Discontinued from study*	12 (8.4)	4 (2.9)	16 (5.7)

* Treated patients who did not complete the second-look procedure.

[6] Reproduced from Table 6.4 of the Clinical Trial Report, March 4, 1999

A list of treated patients who discontinued from the study and the reasons for discontinuation is provided in Table 5.5.

Table 5.5
PATIENTS WHO DISCONTINUED FROM THE STUDY AND THE REASON FOR DISCONTINUATION[7]

Patient Identification	Site No.	Reason for Discontinuation
Patients randomized to INTERGEL® Solution		
[redacted]	2	Patient Decision - patient had no complaints but refused second-look
[redacted]	2	Patient Decision - patient had mild supra-pubic pain but refused second-look due to move
[redacted]	2	Physician Decision - failed laparoscopy due to patient obesity
[redacted]	5	Patient Decision - patient had no complaints but refused second-look
[redacted]	11	Pregnant
[redacted]	11	Patient Decision - patient had no complaints but refused second-look
[redacted]	11	Patient Decision - patient had a pleural effusion after the surgery, did not want any more complications, and refused second-look
[redacted]	11	Patient Decision - patient refused second-look and refused to complete her medication diaries
[redacted]	12	Patient Decision - patient had no complaints but refused second-look due to personal reasons
[redacted]	21	Patient Decision - patient was feeling well and did not want a second-look
[redacted]	21	Patient Decision - patient was feeling well and did not want a second-look
[redacted]	23	Lost to Follow-up - patient did not return verbal or written messages to schedule the second-look
Patient randomized to lactated Ringer's solution		
[redacted]	2	Patient Decision - patient had some lower quadrant pain but refused second-look due to out-of-state move
[redacted]	2	Patient Decision - patient thought she had not fully recovered from first surgery, had returned to work, but refused second-look
[redacted]	12	Patient Decision - patient refused second-look because she thought surgery involving her belly button would make her infertile. She brought her minister with her to Dr. office and even he was unable to educate her regarding this matter.
[redacted]	21	Patient Decision - patient was feeling well and did not want a second-look

[7] Reproduced from Table 6.5 of the Clinical Trial Report, March 4, 1999

5.2 ANALYSIS OF EFFICACY DATA

All 265 patients (131 INTERGEL® Solution and 134 lactated Ringer's solution patients) who completed the second-look laparoscopic procedure were included in the efficacy analysis, and comprise the evaluable patient population. All results presented utilized this efficacy data set unless otherwise specified.

5.2.1 Demographic and Baseline Features of Patients and Comparability of Treatment Groups

Patients in the INTERGEL® Solution and lactated Ringer's solution groups were compared with respect to demographics, baseline surgical procedures, baseline operative characteristics, baseline adhesion data, and baseline laboratory values.

5.2.1.1 Demographics, Height, Weight, and Vital Signs

Patients in the two treatment groups were comparable with respect to race, age, height, weight, and vital signs with no statistically significant differences between the two groups (Table 5.6).

Table 5.6
DEMOGRAPHICS, HEIGHT, WEIGHT, AND VITAL SIGNS[8]

Variable	INTERGEL® Solution n	N	%	Lactated Ringer's Solution n	N	%	p*
Race							0.830
Caucasian	74	131	56.5%	82	134	61.2%	
Black	28	131	21.4%	23	134	17.2%	
Oriental	4	131	3.1%	4	134	3.0%	
Hispanic	20	131	15.3%	22	134	16.4%	
Other	5	131	3.8%	3	134	2.2%	

Variable	N	Mean	(SD)	Range	N	Mean	(SD)	Range	p
Age (years)	131	33.8	(5.8)	18.8 to 44.9	134	34.2	(5.4)	18.6 to 45.9	0.637
Temperature (F)	125	98.1	(0.8)	95.9 to 99.9	131	98.3	(0.6)	96.0 to 99.7	0.079
Pulse (bpm)	128	75.1	(11.2)	45 to 110	132	74.8	(10.9)	50 to 109	0.811
Respiration (min)	114	18.3	(3.7)	10 to 32	113	19.2	(6.1)	10 to 64	0.174
Systolic BP (mmHg)	131	120.1	(14.5)	92 to 162	133	119.9	(13.9)	80 to 168	0.900
Diastolic BP (mmHg)	131	73.7	(11.1)	47 to 108	133	73.7	(10.6)	42 to 104	0.998
Height (in)	130	64.5	(2.5)	57.0 to 71.0	134	64.6	(2.9)	57.0 to 71.7	0.690
Weight (lbs)	131	150.1	(30.9)	104 to 252	134	150.2	(31.8)	100 to 264	0.994

*p values determined using the Fisher exact test for categorical variables or Student's t-test for continuous variables

[8] Adapted from Table 8.3 of the Clinical Trial Report, March 4, 1999 (performed new overall analysis of statistical significance)

5.2.1.2 Operative Characteristics

Operative characteristics, including blood loss, operative time, days to discharge, days to second-look laparoscopy, presence of adhesions, and presence of endometriosis, were similar in the two treatment groups with no statistically significant differences between the groups (Table 5.7).

Table 5.7
OPERATIVE CHARACTERISTICS[9]

Variable	INTERGEL® Solution n	N	%	Lactated Ringer's Solution n	N	%	p*
Adhesions	70	131	53.4%	71	134	53.0%	1.000
Endometriosis	23	131	17.6%	29	134	21.6%	0.381
Stage I	9	23	39.1%	9	29	31.0%	
Stage II	4	23	17.4%	11	29	37.9%	
Stage III	4	23	17.4%	5	29	17.2%	
Stage IV	6	23	26.1%	4	29	13.8%	
Transfusions	8	131	6.1%	4	134	3.0%	0.251

Variable	N	Mean	(SD)	Range	N	Mean	(SD)	Range	p
Blood Loss (mL)	131	214	(214)	2 to 1500	134	224	(284)	2 to 2200	0.742
Blood Units	131	0.15	(0.66)	0.00 to 4.00	134	0.08	(0.49)	0.00 to 4.00	0.324
Oper Time (hrs)	131	1.86	(0.82)	0.75 to 5.00	134	1.80	(0.85)	0.75 to 5.00	0.533
Days to Discharge	131	3.0	(1.6)	0 to 12	134	3.0	(1.7)	0 to 10	0.909
Days to 2nd Look	131	60.4	(26.2)	26 to 245	134	58.7	(21.4)	31 to 145	0.561

*p values determined using the Fisher exact test or Student's t-test

[9] Adapted from Table 8.4 of the Clinical Trial Report, March 4, 1999 (performed new overall analysis of statistical significance)

5.2.1.3 Surgical Procedures

Similar surgical procedures were performed in the two treatment groups with no statistically significant differences between the groups (Table 5.8). Myomectomy, adhesiolysis, ovarian surgery, and tubal surgery were the four most common procedures.

Table 5.8
SURGICAL PROCEDURES[10]

Variable	INTERGEL® Solution n	N	%	lactated Ringer's Solution n	N	%	p*
APPENDECTOMY	1	131	0.8%	0	134	0.0%	0.494
LAPAROTOMY	131	131	100.0%	134	134	100.0%	1.000
ABLATION ENDOMETRIOSIS	13	131	9.9%	18	134	13.4%	0.446
CYSTOTOMY REPAIR	1	131	0.8%	1	134	0.7%	1.000
OMENTECTOMY	0	131	0.0%	1	134	0.7%	1.000
LAPAROSCOPY	2	131	1.5%	4	134	3.0%	0.684
HYSTEROSCOPY	5	131	3.8%	6	134	4.5%	1.000
HYSTEROSCOPY / LYSIS	3	131	2.3%	0	134	0.0%	0.119
HYSTEROSCOPY / RESECTION	1	131	0.8%	0	134	0.0%	0.494
EXCISION VAGINAL CYST	0	131	0.0%	1	134	0.7%	1.000
COLPOSCOPY	0	131	0.0%	1	134	0.7%	1.000
ENDOMETRIAL BIOPSY	1	131	0.8%	0	134	0.0%	0.494
DILATION AND CURETTAGE	3	131	2.3%	1	134	0.7%	0.367
MYOMECTOMY	88	131	67.2%	92	134	68.7%	0.895
CHROMOPERTUBATION	2	131	1.5%	7	134	5.2%	0.172
UTERINE SUSPENSION	2	131	1.5%	1	134	0.7%	0.619
UTERINE SUSPENSION / NEURECTOMY	0	131	0.0%	1	134	0.7%	1.000
SALPINGO-OOPHORECTOMY	1	131	0.8%	0	134	0.0%	0.494
ADHESIOLYSIS	66	131	50.4%	65	134	48.5%	0.806
TUBAL REVERSAL	2	131	1.5%	2	134	1.5%	1.000
FIMBRIOPLASTY	4	131	3.1%	9	134	6.7%	0.255
SALPINGOSTOMY	17	131	13.0%	13	134	9.7%	0.442
PARATUBAL CYSTECTOMY	8	131	6.1%	4	134	3.0%	0.251
OVARIAN RESECTION	4	131	3.1%	1	134	0.7%	0.210
OVARIAN CYSTECTOMY -SIMPLE	12	131	9.2%	13	134	9.7%	1.000
OVARIAN CYSTECTOMY -DERMOID	3	131	2.3%	8	134	6.0%	0.217
OVARIAN CYSTECTOMY -ENDOMETRIOMA	13	131	9.9%	10	134	7.5%	0.519
OVARIAN SUSPENSION	0	131	0.0%	1	134	0.7%	1.000

*p values determined using the Fisher Exact test

[10] Reproduced from Table 8.5 of the Clinical Trial Report, March 4, 1999

5.2.1.4 Baseline Adhesion Assessment

There were no statistically significant differences between the two treatment groups for any of the baseline adhesion variables (see Table 5.9). Prior to any surgical intervention the number and proportion of sites with adhesions, and the extent, severity, and AFS adhesion scores were similar for the two treatment groups. The number of adhesions lysed and the total number of surgical sites were also similar. Thus, the number of adhesions which were present at baseline and not lysed were also similar. An adjusted baseline comparison, with non-lysed adhesions removed indicates the two groups were similar with respect to the number and proportion of sites with adhesions, as well as the extent and severity.

Table 5.9
BASELINE ADHESION DATA[11]

Variable	INTERGEL® Solution N	Mean	(SD)	Range	Lactated Ringer's Solution N	Mean	(SD)	Range	p
Pre-Surgical Baseline									
Adhesions	131	3.65	(4.27)	0 to 15	134	3.46	(4.41)	0 to 14	0.727
Total Possible	131	22.82	(0.77)	18 to 23	134	22.66	(1.12)	18 to 23	0.157
Proportion	131	0.161	(0.187)	0.00 to 0.65	134	0.156	(0.201)	0.00 to 0.78	0.853
Severity Score(0-3)	131	0.38	(0.49)	0.0 to 1.9	134	0.35	(0.47)	0.0 to 1.7	0.517
Extent Score(0-3)	131	0.29	(0.39)	0.0 to 1.5	134	0.30	(0.40)	0.0 to 1.6	0.917
AFS Score (0-32)	131	2.44	(5.32)	0.0 to 32.0	134	2.85	(6.04)	0.0 to 32.0	0.553
Surgical Interventions									
Adhesions Lysed	131	3.07	(3.84)	0 to 15	134	2.92	(4.05)	0 to 14	0.756
Surgical Sites	131	5.53	(3.46)	2 to 16	134	5.48	(3.55)	2 to 15	0.895
Post-Laparotomy Baseline									
Adhesions	131	0.58	(1.47)	0 to 8	134	0.54	(1.39)	0 to 6	0.840
Total Possible	131	22.82	(0.77)	18 to 23	134	22.66	(1.12)	18 to 23	0.157
Proportion	131	0.026	(0.064)	0.00 to 0.35	134	0.026	(0.066)	0.00 to 0.33	0.995
Severity Score(0-3)	131	0.07	(0.18)	0.0 to 1.0	134	0.07	(0.17)	0.0 to 0.9	0.945
Extent Score(0-3)	131	0.05	(0.13)	0.0 to 0.8	134	0.05	(0.14)	0.0 to 0.8	0.783
AFS Score(0-32)	131	0.18	(1.20)	0.0 to 8.0	134	0.16	(1.14)	0.0 to 12.0	0.854
Adjusted Baseline									
Adhesions	131	3.07	(3.84)	0 to 15	134	2.92	(4.05)	0 to 14	0.756
Total Possible	131	22.24	(1.71)	15 to 23	134	22.11	(2.10)	12 to 23	0.575
Proportion	131	0.141	(0.173)	0.00 to 0.65	134	0.137	(0.189)	0.00 to 0.69	0.864
Severity Score(0-3)	131	0.33	(0.44)	0.0 to 1.9	134	0.29	(0.44)	0.0 to 1.6	0.504
Extent Score(0-3)	131	0.26	(0.35)	0.0 to 1.5	134	0.26	(0.37)	0.0 to 1.5	0.976

p values determined using Student's t-test

[11] Adapted from Table 9.4 of the Panel Pack Clinical Summary (mAFS data omitted, pre-surgical adhesions and severity of adhesions 1-3 omitted)

5.2.1.5 Baseline Laboratory Values

The baseline clinical laboratory mean values were not significantly different between the two treatment groups, as shown in Table 5.10 on the following page.

Table 5.10
BASELINE LABORATORY VALUES[12]

Variable	Lubricoat Gel N	Mean	(SD)	Range	Lactated Ringer's Solution N	Mean	(SD)	Range	p
BUN (mg/dL)	142	11.15	(3.14)	5.0 to 22.0	137	11.57	(3.28)	4.8 to 21.8	0.277
Creatinine (mg/dL)	143	0.80	(0.14)	0.5 to 1.3	136	0.79	(0.14)	0.5 to 1.2	0.760
Phosphorus (mg/dL)	140	3.50	(0.58)	2.2 to 5.4	131	3.55	(0.58)	1.7 to 5.3	0.466
Calcium (mg/dL)	142	9.38	(0.52)	7.2 to 10.8	135	9.43	(0.53)	8.3 to 11.5	0.418
Uric Acid (mg/dL)	140	3.79	(1.07)	1.3 to 7.2	131	3.80	(1.06)	1.8 to 7.0	0.956
Total Protein (gm/dl)	138	7.24	(0.56)	4.7 to 8.4	133	7.33	(0.56)	5.1 to 8.7	0.169
Albumin (gm/dl)	143	4.26	(0.43)	2.6 to 5.3	137	4.29	(0.39)	3.2 to 5.4	0.580
Total Bilirubin (mg/dL)	143	0.52	(0.24)	0.2 to 1.9	137	0.52	(0.24)	0.1 to 1.8	0.908
SGOT (IU/L)	143	20.2	(10.8)	8 to 119	137	21.8	(10.5)	7 to 85	0.195
SGPT (IU/L)	141	19.5	(11.8)	3 to 77	134	22.4	(14.7)	7 to 127	0.068
Alkaline Phosphatase (IU/L)*	143	74.8	(39.9)	25 to 246	136	77.2	(42.0)	29 to 258	0.631
Sodium (mEq/L)	143	140.0	(2.1)	135 to 148	138	139.9	(2.5)	132 to 148	0.595
Potassium (mEq/L)	143	4.13	(0.30)	3.3 to 4.9	138	4.20	(0.42)	3.1 to 5.8	0.158
Chloride (mEq/L)	142	105.2	(3.7)	96 to 126	138	105.2	(4.2)	97 to 124	0.891
Hemoglobin (g/dL)	141	12.72	(1.40)	8.0 to 15.3	137	12.85	(1.24)	8.6 to 16.0	0.412
Hematocrit (%)	141	37.9	(4.1)	24.0 to 46.5	137	38.4	(3.6)	26.4 to 48.4	0.332
RBC (mil/cu.mm)	141	4.32	(0.39)	3.38 to 5.30	137	4.36	(0.43)	3.44 to 5.53	0.383
WBC (thous/cu.mm)	141	6.62	(1.85)	3.6 to 14.8	137	6.83	(2.25)	2.8 to 18.1	0.402
Neutrophils (%)	132	57.9	(8.7)	29.6 to 76.9	125	59.6	(11.1)	31.0 to 89.0	0.181
Lymphocytes (%)	132	31.7	(7.3)	17.0 to 50.9	126	30.2	(9.6)	7.0 to 53.0	0.152
Monocytes (%)	132	7.0	(2.1)	2.0 to 14.0	126	6.8	(2.2)	1.7 to 13.0	0.583
Eosinophils (%)	132	2.4	(1.8)	0.0 to 11.3	126	2.3	(2.1)	0.0 to 10.8	0.882
Basophils (%)	132	0.7	(0.4)	0.0 to 2.0	126	0.7	(0.5)	0.0 to 3.0	0.859

Variable	n	N	%	n	N	%	p
Clinically Significant	0	137	0.0%	1	134	0.7%	0.494
Pregnancy	0	143	0.0%	0	137	0.0%	0.494

p values determined using Student's t-test or the Fisher exact test
* Alkaline Phosphatase values could not be adequately transformed for some centers

[12] Reproduced from Table 7.1 (supplemental tables) of the Clinical Trial Report, March 4, 1999

5.2.2 Primary Efficacy Analysis of Adnexal Adhesions

Adnexal adhesions in the two treatment groups were scored according to the AFS scoring system. As previously described, the AFS adhesion scoring method as originally conceived was designed to provide a systematic means of evaluating adnexal adhesion, thereby taking into account only the ovaries and fallopian tubes. Appendix A provides examples of case report forms and a flow chart describing the determination of the AFS adhesion score from the source documents in the INTERGEL® Solution pivotal trial.[13]

Data on AFS adhesion scores for adnexal adhesions were presented in the original Study Report (Appendix D). For data on adhesions scored in this trial at sites other than the adnexa utilizing the systematic approach developed by the AFS, the reader is referred to the same report.

5.2.2.1 Comparison of Adhesion Classification Groups

As illustrated in Table 5.11, the INTERGEL® Solution patients had a greater proportion of patients with minimal adhesions at second-look compared to lactated Ringer's solution patients (92.4% vs. 78.4%), and a smaller proportion of patients with mild adhesions (5.3% vs. 9.0%), moderate adhesions (1.5% vs. 7.5%), and severe adhesions (0.8% vs. 5.2%).

The proportion of patients with minimal AFS scores (score 0-5) increased in the patient group that received INTERGEL® Solution (from 83.2% at baseline to 92.4% at second-look) as shown in Table 5.11. In contrast, the proportion of patients who received lactated Ringer's solution who had minimal AFS scores at baseline decreased at second-look (from 81.3% at baseline to 78.4% at second-look). Similarly, the proportion of patients with mild, moderate and severe AFS scores decreased in the group that received INTERGEL® Solution and increased in the group that received lactated Ringer's solution.

[13] The original protocol for this trial included a quality assurance step in which a blinded medical reviewer assessed videotapes of second-look laparoscopy in order to compare and reconcile if necessary any discrepancies in the adhesion scores provided by the study investigators. The present analysis is based on original source data, and does not include any reconciliation by the independent medical reviewer, per FDA preference.

Table 5.11
AFS CLASSIFICATION AT BASELINE AND SECOND-LOOK LAPAROSCOPY[14]

Variable			INTERGEL® Solution n / N	%	Lactated Ringer's Solution n / N	%	p
Proportions							
Baseline	0-5	(minimal)	109 / 131	83.2%	109 / 134	81.3%	
	6-10	(mild)	13 / 131	9.9%	8 / 134	6.0%	
	11-20	(moderate)	7 / 131	5.3%	13 / 134	9.7%	
	21-32	(severe)	2 / 131	1.5%	4 / 134	3.0%	
							0.315
Second Look	0-5	(minimal)	121 / 131	92.4%	105 / 134	78.4%	
	6-10	(mild)	7 / 131	5.3%	12 / 134	9.0%	
	11-20	(moderate)	2 / 131	1.5%	10 / 134	7.5%	
	21-32	(severe)	1 / 131	0.8%	7 / 134	5.2%	
							0.005

p values determined using the Fisher exact test

[14] Adapted from Table 9.43 of the Panel Pack Clinical Summary (mean values omitted; performed new overall analysis of statistical significance)

5.2.2.2 Shift Tables: Primary Analysis Presented as Success/Failure

A moderate or severe AFS adhesion score at second-look was considered a treatment failure in this study. Table 5.12 presents baseline and second-look results for all four AFS adhesion categories (upper part of table), followed by the analysis of treatment success/failure (binary analysis, lower part of table).

As indicated, 109 patients in the INTERGEL® Solution group had a baseline AFS adhesion score in the minimal category. Of these, 103 remained in the minimal AFS category at second-look, while 4 became mild, and 1 each became moderate and severe. In the control group, 109 patients also had a baseline AFS score in the minimal category, but fewer (96) of the 109 patients remained in the minimal category at second-look, while 6 became mild, 3 became moderate and 4 became severe. Analysis using the Cochran-Mantel-Haenszel test controlling for baseline level indicates a highly significant p value ($p = 0.001$) between treatment groups in the shift of patients from one AFS adhesion category to another.

In the analysis of treatment success/failure (binary analysis), 3 of 122 INTERGEL® Solution patients (2.5%) shifted from the minimal/mild category to the moderate/severe category compared to 10 of 117 control patients (8.5%). All nine patients in the INTERGEL® Solution group (100%) that started off in the moderate/severe category improved (moved to the minimal/mild group) compared to only 10 of 17 control patients (59%). Analysis using the Cochran-Mantel-Haenszel test controlling for baseline level indicates a highly significant p value ($p = 0.003$) with regard to the difference in treatment success/failure. Overall, 3 patients in the INTERGEL® Solution group (2.3%) had moderate or severe adhesion scores at second-look, compared to 17 (12.7%) patients in the control group. Based on these data, the relative risk of treatment failure in the control group is 5 times that of the INTERGEL® Solution group.

Supplementary analyses of this primary binary endpoint (treatment success/failure) were performed to explore the impact of the 16 patients who had no second-look laparoscopy. Data was imputed for subjects with incomplete ascertainment under several different scenarios as described in Section 4.0, Analysis of Incomplete Ascertainment Subject Data. The results of these analyses support the demonstration of the effectiveness of INTERGEL® Solution as in the primary binary analysis presented in Table 5.12.

Table 5.12
SHIFT TABLE FOR PRIMARY ANALYSIS OF AFS CLASSIFICATION (FAILURE RATES)[15]

Four Category Analysis			INTERGEL® Solution					Lactated Ringer's Solution					
				---- Second Look -----					---- Second Look -----				
			Baseline Total	Min. 0-5	Mild 6-10	Mod. 11-20	Sev. 21-32	Baseline Total	Min. 0-5	Mild 6-10	Mod. 11-20	Sev. 21-32	p
Unadjusted	Minimal	0-5	109	103	4	1	1	109	96	6	3	4	
	Mild	6-10	13	10	2	1	0	8	4	1	2	1	
	Moderate	11-20	7	6	1	0	0	13	3	4	5	1	
	Severe	21-32	2	2	0	0	0	4	2	1	0	1	
	Total Second-Look		131	121	7	2	1	134	105	12	10	7	0.001* 0.001**

Binary Analysis									
				--- Second Look ----			--- Second Look ----		
			Baseline Total	Min./Mild 0-10	Mod./Sev. 11-32	Baseline Total	Min./Mild 0-10	Mod./Sev. 11-32	p
Unadjusted	Min./Mild	0-10	122	119	3	117	107	10	0.003
	Mod./Sev.	11-32	9	9	0	17	10	7	
	Total Second-Look		131	128	3	134	117	17	
	Relative Risk (INTERGEL® Solution/Control): 0.195 95% CI: 0.065 to 0.583								

* p value determined using CMH test controlling for Baseline level (ridit scores)
** p value determined using CMH test controlling for Baseline level (median scores)

[15] Adapted from Table 9.44 of the Panel Pack Clinical Summary (performed new overall analysis of statistical significance)

5.2.2.3 Stratified Binary Analysis

The binary analysis of the AFS data can also be stratified to take into consideration any baseline differences between the U.S. and the European cohorts. Pooling of U.S. and European data is justified based on consideration of all arguments presented in Section 3.0, Justification for Use of Data from All Trial Sites. However, to take into consideration any differences between the continent and adhesioloysis subgroup strata, the primary analysis of success/failure was stratified by these variables. All stratified analyses remained statistically significant as shown in Table 5.13. The impact of INTERGEL® Solution was not diminished by continent or by adhesiolyisis.

Table 5.13

PERCENTAGE OF PATIENTS WITH MODERATE OR SEVERE SCORES AT SECOND-LOOK (STRATIFIED BY CONTINENT OF ENROLLMENT AND ADHESIOLYSIS CATEGORY)

			INTERGEL® Solution		Lactated Ringers		Relative		
Continent	Adhesiolysis	Center	n / N	Percent	n / N	Percent	Risk	95% CI	p
U.S.	None	All	1/ 58	1.7	4/ 58	6.9	0.250	0.034 to 1.828	0.1721
U.S.	Minimal/Mild	All	2/ 30	6.7	4/ 30	13.3	0.500	0.102 to 2.456	0.3934
U.S.	Moderate/Severe	All	0/ 5	0.0	3/ 7	42.9	0.000		0.1056
Europe	None	All	0/ 7	0.0	0/ 11	0.0			
Europe	Minimal/Mild	All	0/ 27	0.0	2/ 18	11.1	0.000		0.0798
Europe	Moderate/Severe	All	0/ 4	0.0	4/ 10	40.0	0.000		0.1492
All*	All*	All	3/131	2.3	17/134	12.7	0.198	0.067 to 0.581	0.0032
All	None	All	1/ 65	1.5	4/ 69	5.8	0.265	0.036 to 1.976	0.1953
All	Minimal/Mild	All	2/ 57	3.5	6/ 48	12.5	0.281	0.066 to 1.192	0.0851
All	Moderate/Severe	All	0/ 9	0.0	7/ 17	41.2	0.000		0.0272
All	All**	All	3/131	2.3	17/134	12.7	0.188	0.063 to 0.560	0.0027
All	All	All***	3/131	2.3	17/134	12.7	0.181	0.063 to 0.516	0.0014

Blanks indicate that the value could not be calculated, p values: Cochran-Mantel-Haenszel Test, Relative Risk: Mantel-Haenszel Method

* Stratified by Continent and Adhesiolysis Category (Breslow-Day test of Homogeneity: p = 0.5682)

** Stratified by Adhesiolysis Category (Breslow-Day test of Homogeneity: p = 0.4985)

*** Not Stratified

5.2.2.4. Subgroup Analysis by Surgical Procedure

A subgroup analysis by surgical procedure indicates that those patients most likely to benefit from INTERGEL® Solution were those undergoing adhesiolysis and myomectomy procedures as shown in Table 5.14. For those patients who underwent myomectomies, the percentage of treatment failures (patients with moderate or severe adhesions at second-look) was significantly reduced from 9.8% to 2.3% (p=0.036) in the INTERGEL® Solution group. The percentage of patients with treatment failures (moderate to severe adhesions at second-look) was significantly reduced from 20.0% to 3.0% (p=0.006) in the INTERGEL® Solution group for patients undergoing adhesiolysis procedures. Patients who underwent tubal procedures, ovarian procedures, and ablation of endometriosis also showed favorable trends with INTERGEL® Solution.

Table 5.14
SHIFT TABLES FOR AFS PROGNOSTIC CLASSIFICATION: SURGICAL SUBGROUPS

Procedure Subgroup	AFS Classification	INTERGEL® Solution				Lactated Ringer's Solution				p	Relative Risk
		Baseline	Second Look Min/Mild	Second Look Mod/Sev	% Failure	Baseline	Second Look Min/Mild	Second Look Mod/Sev	% Failure		
All Patients	Min/Mild	122	119	3		117	107	10			
	Mod/Sev	9	9	0		17	10	7			
	Total	131	128	3	2.3%	134	117	17	12.7%	0.003	0.195
Myomectomy	Min/Mild	85	83	2		89	80	9			
	Mod/Sev	3	3	0		3	3	0			
	Total	88	86	2	2.3%	92	83	9	9.8%	0.036	0.233
No Myomectomy	Min/Mild	37	36	1		28	27	1			
	Mod/Sev	6	6	0		14	7	7			
	Total	43	42	1	2.3%	42	34	8	19.0%	0.067	0.161
Adhesiolysis	Min/Mild	57	55	2		48	42	6			
	Mod/Sev	9	9	0		17	10	7			
	Total	66	64	2	3.0%	65	52	13	20.0%	0.006	0.161
No Adhesiolysis	Min/Mild	65	64	1		69	65	4			
	Mod/Sev	0	0	0		0	0	0			
	Total	65	64	1	1.5%	69	65	4	5.8%	0.195	0.265
Tubal Procedures	Min/Mild	14	14	0		9	9	0			
	Mod/Sev	6	6	0		11	6	5			
	Total	20	20	0	0	20	15	5	25.0%	0.057	*
Ovarian Procedures	Min/Mild	27	26	1		26	24	2			
	Mod/Sev	4	4	0		7	2	5			
	Total	31	30	1	3.2%	33	26	7	21.2%	0.049	0.173
Ablation Endometriosis	Min/Mild	23	22	1		24	21	3			
	Mod/Sev	1	1	0		2	0	2			
	Total	24	23	1	4.2%	26	21	5	19.2%	0.131	0.239

* Relative risk cannot be calculated because no failures (patients with mod/sev at second-look) occurred in the INTERGEL® Solution group.

5.2.3 Secondary Analyses

In addition to the analysis of adhesion prevention based on the AFS adhesion score applied to the adnexa, analysis of surgical site adhesions and reformed adhesions were also included in the original report of this clinical trial, and are provided in this amendment as supportive evidence of efficacy.

5.2.3.1 Proportion of Surgical Site Adhesions

For each patient, the proportion of the surgical sites that had adhesions was determined at both baseline and at second-look laparoscopy, regardless of whether or not adhesions had been lysed at baseline (each patient had at least one surgical site, the site of incision). While the number of surgical sites was similar for the two groups at baseline (Table 5.9), the proportion of surgical sites with adhesions was significantly reduced (p=.003) from 0.500 in the lactated Ringer's group to 0.386 in the INTERGEL® Solution group, a 23% reduction (Table 5.15).

5.2.3.2 Proportion of Reformed Adhesions

Similarly, the proportion of sites with reformed adhesions were assessed for each patient. Reformed adhesions were those that were lysed at first surgery that had reformed at second look. While the number of adhesions lysed was similar for the two groups at baseline (Table 5.9), the proportion of sites with reformed adhesions was significantly reduced (p=.001) from 0.663 in the lactated Ringer's group to 0.459 in the INTERGEL® Solution group, a 31% reduction (Table 5.15).

Table 5.15
SURGICAL SITE ADHESIONS AND REFORMED ADHESIONS[16]

	INTERGEL® Solution				Lactated Ringer's Solution				
Variable	N	Mean	(SD)	Range	N	Mean	(SD)	Range	p
Surgical site Adhesions	131	2.27	(2.46)	0 to 12	134	2.96	(2.91)	0 to 13	0.039
Total Possible	131	5.53	(3.46)	2 to 16	134	5.48	(3.55)	2 to 15	0.895
Proportion	131	0.386	(0.312)	0.00 to 1.00	134	0.500	(0.302)	0.00 to 1.00	0.003
Severity Score(0-3)	131	0.78	(0.76)	0.0 to 3.0	134	1.14	(0.84)	0.0 to 3.0	0.000
Extent Score(0-3)	131	0.64	(0.66)	0.0 to 3.0	134	0.97	(0.75)	0.0 to 3.0	0.000
Reformed Adhesions	66	2.97	(2.67)	0 to 12	65	3.91	(3.12)	0 to 12	0.066
Total Possible	66	6.09	(3.29)	1 to 15	65	6.02	(3.90)	1 to 14	0.905
Proportion	66	0.459	(0.336)	0.00 to 1.00	65	0.663	(0.351)	0.00 to 1.00	0.001
Severity Score(0-3)	66	0.94	(0.81)	0.0 to 3.0	65	1.47	(1.03)	0.0 to 3.0	0.002
Extent Score(0-3)	66	0.82	(0.76)	0.0 to 2.7	65	1.32	(0.88)	0.0 to 3.0	0.001

p values determined using Student's t-test

[16] Adapted from Table 9.8 of the Panel Pack Clinical Summary (includes new analysis based on the proportion of surgical adhesions determined at both baseline and at second-look)

6.0 CONCLUSIONS

This randomized, multi-center, double-blind clinical trial of INTERGEL® Solution provides a high-quality source of data on the incidence, extent, and severity of post-surgical adhesions following gynecological pelvic surgery. The trial utilized a systematic means of assessing adhesions (the AFS adhesion scoring system applied to 24 sites throughout the peritoneal cavity). A subset of the data from this trial (narrowed to consider only certain sites, but inclusive of all subjects) has been presented again, with additional statistical analyses, consideration of concerns regarding clinical utility, and within the context of a revised indication for use.

The data provided in this amendment indicate that INTERGEL® Solution reduces the incidence of adnexal adhesions when used as an intraperitoneal instillate following conservative gynecological pelvic surgery, as an adjunct to good surgical technique. INTERGEL® Solution is more effective than lactated Ringer's solution as revealed by shift tables for minimal and mild vs. moderate and severe combined AFS classifications. This endpoint (moderate/severe adhesions) is well-correlated with a poor fertility prognosis. Significantly fewer INTERGEL® Solution patients with minimal or mild adhesions at baseline had moderate or severe adhesions at second-look compared to lactated Ringer's patients. The magnitude of this effect is clinically significant with the INTERGEL® Solution group showing a 5-fold lower rate of treatment failure (moderate or severe adhesions at second-look) compared to controls. Additionally, all patients in the INTERGEL® Solution group (100%) that had moderate/severe adhesions at baseline improved at second-look to minimal/mild, compared to 59% of control patients.

Clinical benefit was seen in a subgroup analysis of patients by surgical category, with statistical significance seen in patients undergoing myomectomy or adhesiolysis. In addition, trends for greater benefit with INTERGEL® Solution were seen in patients undergoing ovarian and tubal surgeries and ablation of endometriosis.

Finally, INTERGEL® Solution provides clinical benefit beyond the adnexa, as demonstrated by secondary efficacy endpoints. Compared to lactated Ringer's solution, INTERGEL® Solution significantly reduced the proportion of surgical site adhesions as well as the proportion of reformed adhesions.

These data, in combination with a consideration of the evidence on safety, provide reasonable assurance that INTERGEL® Solution is safe and effective for the proposed intended use.

7.0 REFERENCES

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